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Depression doubles the likelihood of comorbid depression, which presents as major depression in 11% and subsyndromal depression in 31% of patients with the medical illness. The course of depression is chronic, and afflicted patients suffer an average of one episode annually. Depression has unique importance in diabetes because of its association with poor glycemic control, treatment nonadherence, and increased risk for complications of the metabolic disorder. Linkage with coronary heart disease is particularly strong--an association established in prospective and cross-sectional studies and most pronounced in diabetic women. While the number of available controlled depression treatment trials in diabetic patients is small, both pharmacological and psychotherapeutic approaches appear effective. Relief of depression also produces clinically significant improvements in glycemic control. Extant diabetes complications and hyperglycemia diminish responsiveness to antidepressant treatment and increase the risk for recurrence of depression. These observations suggest that concurrent management of both diabetes and depression is needed to optimize outcomes from depression treatment. (Contains 43 references and 3 figures.) (Author)

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Importance of Depression in Diabetes

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Abstract

Diabetes doubles the likelihood of comorbid depression, which presents as major depression in 11% and as subsyndromal depression in 31% of patients with the medical illness. The course of depression is chronic, and afflicted patients suffer an average of one episode annually. Depression has unique importance in diabetes because of its association with poor glycemic control, treatment nonadherence, and increased risk for complications of the metabolic disorder. Linkage with coronary heart disease (CHD) is particularly strong—an association established in prospective and cross-sectional studies and most pronounced in diabetic women. While the number of available controlled depression treatment trials in diabetic patients is small, both pharmacological and psychotherapeutic approaches appear effective. Relief of depression also produces clinically significant improvements in glycemic control. Extant diabetes complications and hyperglycemia diminish responsiveness to antidepressant treatment and increase the risk for recurrence of depression. These observations suggest that concurrent management of both diabetes and depression is needed to optimize outcomes from depression treatment.

The Epidemic of Diabetes in the United States

Approximately twenty million adults in the United States have diabetes, but only half are actually diagnosed and treated (National Center for Health Statistics, 1997; U.S.Bureau of the Census, 2000; Harris et al., 1998). Type 2 diabetes accounts for nearly 95% of all cases of diabetes, the remainder being type 1. One million new cases of type 2 diabetes are diagnosed annually, reflecting a greater than five-fold increase in annual incidence over the last 35 years. The most dramatic increase is found in those 30-39 years of age, with nearly a doubling in incidence over the last decade alone.

Depression in the Diabetic Population

The prevalence of depression in the diabetic population may be expressed as point or lifetime estimates of subjects with the psychiatric diagnosis (i.e., the percentage of the population meeting criteria for major depression either presently or at any past time), as the point prevalence of subjects reporting symptoms of depression (defined as the percentage scoring above a defined threshold on a depression rating tool), or as an odds ratio comparing prevalence rates to those in the general population. Anderson *et al.* (Anderson, Freedland, Clouse, & Lustman, 2001) recently reported a meta-analysis of 39 studies measuring depression in adults with diabetes. The point prevalences of major depression and of elevated symptoms of depression were 11% and 31%, respectively. By either method of estimation, depression was significantly more prevalent in women with diabetes than in men, higher in clinic than in community samples, higher when assessed from self-report methods than diagnostic interviews, and similar in type 1 compared to type 2 diabetes. When odds ratios were reviewed, the authors concluded that depression

rates were doubled in patients with diabetes compared to those without, regardless of how depression was assessed (Anderson et al., 2001).

The course of depression in diabetes is chronic and severe, and recurrences are the norm rather than the exception. Once depressed, diabetic patients continue to experience approximately one episode of major depression annually (Lustman, Griffith, Freedland, & Clouse, 1997; Lustman, Griffith, & Clouse, 1988). Of those patients who receive short-term depression treatment, 60% experience a recurrence in the 12-months following discontinuation of treatment and nearly 90% have a recurrence of depression over the ensuing five years.

The cause of depression in diabetes is not well-understood but is likely the product of a complex interaction between physical, psychological, and genetic factors. The most popular theory (the "hardship hypothesis") expresses the clinical sentiment that depression is secondary to the physical illness, the result of hardships imposed by diabetes and its myriad complications. Although the challenges associated with coping with diabetes may contribute to depression, observations from longitudinal and clinical trials do not support the hardship hypothesis as being of sole importance, particularly in type 2 diabetes. In fact, the opposite temporal association has been more consistently observed, namely that depression may promote the expression of diabetes. Two prospective population studies having follow-up intervals of 13 and 8 years uniformly found that depression doubles the risk for type 2 diabetes (Eaton, Armenian, Gallo, Pratt, & Ford, 1996; Kawakami, Takatsuka, Shimizu, & Ishibashi, 1999). The effect was independent of the effects of other traditional risk factors (*e.g.*, age, obesity, family history of diabetes).

Depression may accelerate the onset of type 2 diabetes or worsen established diabetes through its adverse effects on weight and activity level that ultimately contribute to insulin resistance. Recent studies have indeed demonstrated the association between depression and insulin resistance, one that can be manipulated through depression treatment and that is not solely related to weight effects (Okamura et al., 2000; McCarty, 1994; Mueller, Heninger, & McDonald, 1969; Wright, Jacisin, Radin, & Bell, 1978; Nathan, Sachar, & Asnis, 1981). Insulin resistance is the principal mechanism behind type 2 diabetes and could potentially explain the link between depression and type 2 diabetes observed in the two prospective trials mentioned above.

A number of other explanations for the co-occurrence of depression and diabetes have been suggested. An organic etiology for depression, particularly in type 1 diabetes, has been proposed hypothesizing that depression occurs consequent to neurochemical or neurovascular changes associated with diabetes (Trulson & Himmel, 1985; MacKenzie & Trulson, 1978; Popkin, Callies, Lentz, Colon, & Sutherland, 1988). Finally, there is also evidence that depression in diabetes may have a genetic component. Lustman *et al.* demonstrated that there is a greater risk of depression in diabetic patients with a family history of depression than in those without (Lustman, Clouse, Carney, & Griffith, 1987).

Significance of Depression in Diabetes

Major depression has significant and pervasive adverse effects in all persons, including those with diabetes. Such effects include increased functional disability, greater work absenteeism, and increased medical morbidity and mortality (Blazer, Hybels, & Pieper, 2001; von Ammon, Furlanetto, Creech, & Powell, 2001; Schulz, Drayer, &

Rollman, 2002; Wells, Golding, & Burnam, 1988; Koenig, Shelp, Goli, Cohen, & Blazer, 1989; Craig & Van Natta, 1983). Depressed diabetic patients also demonstrate increased use of nonessential health care and mount greater medical expenditures that are independent of illness severity (Jacobson, de Groot, & Samson, 1997; Levenson, Hamer, & Rossiter, 1990). Likewise, depression in diabetes has been associated with a number of factors that influence the course of the medical illness including obesity, substance abuse, smoking, physical inactivity, and nonadherence with a diabetes regimen (Farmer, Locke, Moscicki, & Dannenberg, 1988; Frederick, Frerichs, & Clark, 1988; Anda et al., 1990; Glassman et al., 1990; Haire-Joshu, Heady, Thomas, Schechtman, & Fisher, 1994; Lustman & Clouse, 2002) (**Figure 1**).

Recent meta-analyses of cross-sectional and prospective studies have established that depression is associated both with poor glycemic control and with diabetes complications (Lustman, Anderson, Freedland, de Groot, & Carney, 2000; de Groot, Anderson, Freedland, Clouse, & Lustman, 2001). The average increase in glycosylated hemoglobin attributable to depression approached 1.0%, a clinically significant elevation (Lustman, Freedland, Griffith , & Clouse, 2000). Despite the known effect of depression on health behaviors that may adversely affect diabetes management, the increase in glycosylated hemoglobin related to depression is not conspicuously a result of factors such as obesity or nonadherence.

Depression is also associated with an increased risk of a variety of diabetes complications, including atherosclerosis, sexual dysfunction, nephropathy and neuropathy (effect size ≥0.2 for each) (de Groot et al., 2001). The association of depression with coronary heart disease (CHD) in diabetes warrants specific discussion

because CHD is arguably the most significant consequence of diabetes. Diabetes is an independent risk factor for CHD; the age-adjusted prevalence of CHD in persons with diabetes in the US is between 30% and 51%. The risk of CHD and death from heart disease is 2–4 times greater in men with diabetes and 5–6 times greater in women with compared to those without diabetes. Indeed, atherosclerosis accounts for 75% of all hospitalizations for diabetes complications, and 80% of all deaths in diabetes (Eastman & Keen, 1997; Deedwania, 2002; Aronson & Rayfield, 1998). Depression appears to make a causal contribution to CHD in diabetes. Clouse *et al.* recently reported a ten-year prospective study of women with diabetes who were evaluated annually as part of their participation in a diabetes registry (Clouse et al., 2003). In this sample, major depression accelerated the development of CHD and was retained as an independent predictor of CHD after controlling for other conventional risk factors (**Figure 2**).

Depression Treatment in Diabetic Patients

Until recently, little was known about the treatment of depression in patients with diabetes. The burden of coping with diabetes and genetic factors predisposing the patient to co-morbidity may complicate depression treatment in this population, limiting the generalizability of findings from psychiatric samples (Lustman et al., 1987). With this justification, our group at Washington University began a series of controlled treatment trials in the late 1980s in type 1 and type 2 diabetic patients. These results showed that depression in diabetes can be treated effectively using either conventional pharmacologic or psychotherapeutic approaches and are summarized in the following paragraphs (**Figure 3**).

In a double-blind, placebo-controlled trial of nortriptyline, 57.0% of the subset treated with the active drug achieved remission (n =14) versus 35.7% in the placebo group (n =14) (Lustman et al., 1997). The remission rate in those treated with nortriptyline is similar to that reported in non-diabetic depressed patients seen by primary care physicians (Frank, Karp, & Rush, 1993). In a second pharmacologic trial, 60 diabetic patients with major depression were examined in a blinded, placebo-controlled trial of fluoxetine (Lustman et al., 2000). Reduction in depression symptoms (per the Beck Depression Inventory) and the percentage of patients achieving depression remission were both greater in the fluoxetine-treated subjects. Depression remitted in 48.1% of the fluoxetine-treated patients versus 25.9% of those receiving placebo. Preliminary results from an ongoing randomized, double-blind, placebo-controlled trial of sertraline also show promise in maintaining depression remission in a diabetes population. Following successful treatment of depression using sertraline, patients are randomized to a maintenance regimen of either active medication or placebo and are followed until recurrence or up to 12 months. To date, the proportion of subjects remaining depression-free at one year has been significantly greater in the sertraline-treated group than in the group treated with placebo (65% vs. 42%, respectively, p =0.002) (Lustman *et al.*, unpublished observations).

Psychotherapeutic methods also have been effective in diabetes. Fifty-one patients with type 2 diabetes and major depression entered a controlled treatment trial of cognitive behavioral therapy (CBT) versus usual supportive care (Lustman, Griffith, Freedland, Kissel, & Clouse, 1998). Each treatment group also received intensive diabetic education. At the end of the 10-week trial, 85.0% of the patients treated with CBT had reached full

depression remission versus only 27.3% in the control group. At a 6-month follow-up evaluation, the CBT-treated patients also demonstrated a greater improvement in BDI scores.

Treatment of depression in diabetes has significant effects on glycemic control, the principal factor determining the development and course of diabetes complications. The treatment studies mentioned above measured changes in A1C levels in relation to intervention and to depression response. In the first trial, depression remission was associated with improvement in A1C, but a separate adverse effect of nortriptyline on A1C negated this benefit. Results from the other two trials were more favorable. Treatment with either fluoxetine or CBT resulted in improved glycemic control. Patients treated with fluoxetine experienced a 0.4% decrease in A1C levels (versus 0.07% decrease in placebo, $p = 0.12$), and CBT-treated patients measured a 0.7% decrease in A1C by the study's end (versus a 0.9% increase in placebo, $p = 0.04$). In all three studies, the effects of depression treatment on glycemic control were unrelated to changes in weight, and drug-related effects were factored out in the nortiptyline trial (Lustman et al., 1997; Lustman, Freedland, Griffith, & Clouse, 1999; Lustman et al., 1998).

Conclusion

One-third of patients with diabetes have clinically significant symptoms of depression and 11% qualify for the diagnosis of major depression. The course of depression in this population is chronic. Depression complicates the medical disease by promoting poor glycemic control and increasing the risk of diabetes complications, particularly CHD. The mechanisms involved in the association of depression with

hyperglycemia and CHD have not yet been established. Depression in diabetes is a treatable illness; both pharmacologic and psychotherapeutic treatments are effective and can have positive effects on mood, quality of life, and glycemic control. Thus, depression treatment offers a viable method for improving the course, outcome, and quality of life in those living with diabetes.

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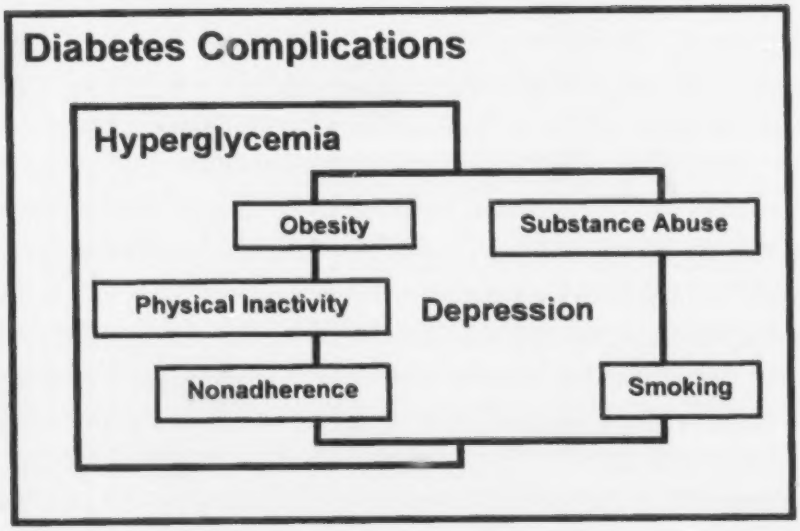

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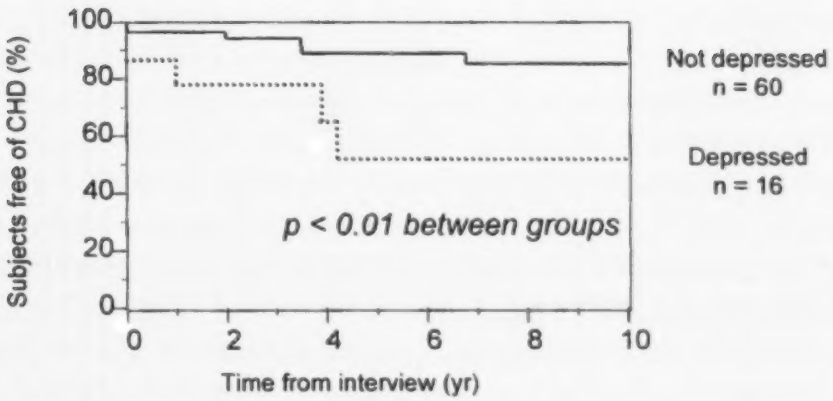
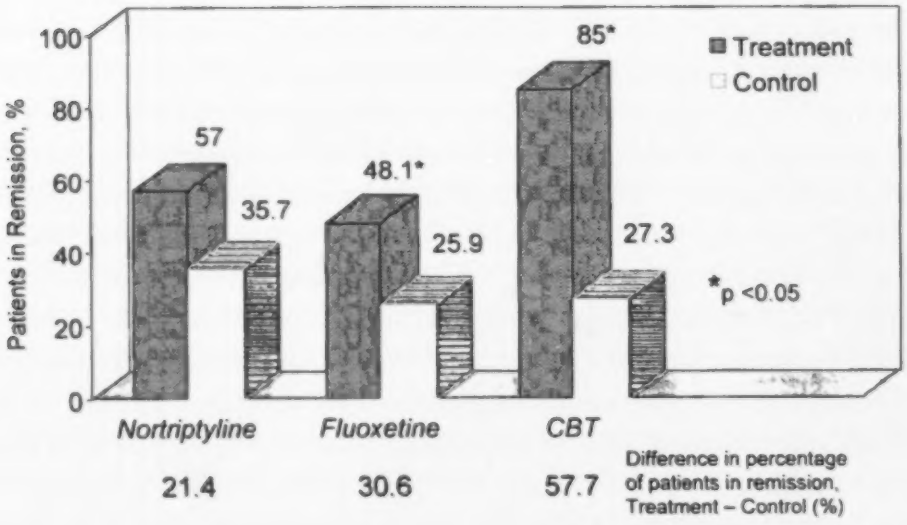

100
80
60
40
20
0
Subjects free of CHD (%)
0
2
4
6
8
10
Time from interview (yr)
p < 0.01 between groups
Not depressed
n = 60
Depressed
n = 16

Figure 3.


100
80
60
40
20
0
Patients in Remission, %
57
35.7
48.1*
25.9
85*
27.3
Treatment
Control
*p <0.05
Nortriptyline
Fluoxetine
CBT
21.4
30.6
57.7
Difference in percentage of patients in remission, Treatment – Control (%)

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